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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/674,666	09/29/2003	Mike Clark	PHOE-0200	5283

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EXAMINER	
LE, EMILY M	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 01/26/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/674,666	CLARK, MIKE	
	Examiner	Art Unit	
	Emily Le	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08/22/2005 and 10/19/2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19,22,25,41,42 and 52-73* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19,22,25,41,42 and 52-73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 7/20/05
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/19/2005 has been entered.

Claims Status

2. Claims 20-21, 23-24, 26-40 and 43-51 are cancelled. Claims 52-73 are added. Claims 1-19, 22, 25, 41-42 and 52-73 are pending and under examination.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-19, 22, 25, 41-42 and 52-73 are rejected under 35 U.S.C. 112, first paragraph for the reasons(s) set forth in the previous office action and below.

As previously indicated, the specification is enabling for a method of inhibiting Hepatitis C viral (HCV) replication in an HCV infected individual comprising administering an effective amount of a composition comprising an arginine deiminase bonded to polyethylene glycol (ADI-PEG) to the individual to inhibit HCV replication in the individual, wherein the individual is infected with HCV genotype 1b and diagnosed

with hepatocellular carcinoma (HCC), which possesses cells that do not express arigininosuccinate synthase (ASS) and are auxotrophic for arginine. However, the specification is not enabling all HCV genotypes, or a population of HCV infected subjects that are free of HCC.

The enablement analysis is as follows:

To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In Genentech *Inc. v. Novo Nordisk* 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997); *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); See also *Amgen Inc. v. Chugai Pharm. Co.,* 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir. 1991); *In re Fisher* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Further, in *In re Wands* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court stated:

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman* [230 USPQ 546, 547 (Bd Pat App Int 1986)]. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The nature of the invention is directed at the use of ADI-PEG to inhibit replication of HCV in a subject infected with HCV.

The breadth of the claims encompasses all HCV genotypes. However, it is clearly demonstrated by Applicant that the claimed invention is not capable of inhibiting the replication of all HCV genotypes. Specifically, the specification discloses that in the presence of hepatocellular carcinoma (HCC) cells, the claimed invention is capable of inhibiting the replication of HCV genotype 1b, but **failed** to inhibit the replication of HCV genotype 2c. [See Table 3 of the disclosure.] Thus, it is evident that the claimed invention is not enabled for inhibition of the replication of all HCV genotypes. This finding is further exemplified by the Bomalaski declaration. In the declaration, Bomalaski provides a summary of the results obtained from recent clinical trials conducted on behalf of Phoenix Pharmacologics, Applicant. The results show that the administration of ADI-PEG to HCV infected subjects that are also diagnosed with HCC **failed** to inhibit the replication of HCV genotypes 2, 2a/2c; 4, 1 and 6a.

The breadth of the claims also encompasses a population of HCV positive subjects that is not diagnosed with HCC. However, the specification does not provide any guidance or teachings showing that ADI-PEG is capable of inhibiting HCV replication in the absence of HCC cells. All that is shown and disclosed in the specification demonstrates that the ADI-PEG is capable of inhibiting HCV replication in the presence of HCC cells, the primary sites for HCV replication.[1]

[1] Fields et al. Fields Virology. Lippincott Williams & Wilkins, 4th Edition, 2001, Vol. 1,1137.

It is noted that Applicant contributes the ability of ADI-PEG to inhibit HCV replication to the lowering of extracellular arginine, which thereby inhibits nitric oxide synthesis. However, it is well known in the art that severing arginine and nitric oxide synthesis leads to the death of HCC cells, exemplified by Izzo et al. Izzo et al. teaches that arginine deiminase kills hepatocellular carcinoma cell lines in vivo and in vitro. [2] Thus, it is gathered that the ability of ADI-PEG to inhibit HCV, genotype 1b replication depends on the synergism that is accorded by the presence of HCC cells. Whether the synergism is solely due to the elimination of the primary site of infection, HCC cells, or combined with other unknown factors, it is found that, the presence of HCC cells is crucial to the operability of Applicant's claimed invention. This is particularly evident by the focus Applicant's endeavor, which is limited to a population of HCC cells. The specification teaches the inhibition of HCV genotype 1b replication with the addition of ADI-PEG in the presence of HCC cells. And the results of recent clinical trials conducted on behalf of Phoenix Pharmacologics, Applicant, show the inhibition of HCV genotype 1b replication with the addition of ADI-PEG in the presence of HCC cells. Nowhere in the clinical trials conducted on behalf of Applicant or the specification has Applicant provided any guidance concerning the success of ADI-PEG in inhibiting HCV replication in the absence of HCC cells.

Moreover, the art also recognizes that antiviral development is not a trivial undertaking. Antiviral development frequently requires *in vitro*, *in vivo*, and preliminary clinical studies to truly ascertain the efficacy of any given antiviral compound, as

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[2] Izzo et al. Pegylated arginine deiminase treatment of patients with unresectable hepatocellular carcinoma: results from Phase I/II studies. Journal of Clinical Oncology. 05/2004, Vol. 22, No. 10, pp. 1815-1822.

evidenced by Oberg et al.[3] Oberg et al. teaches several antiviral drug screening processes, wherein each process is directed at a specific category of viruses. The general outline of each process includes *in vitro* studies, *in vivo* animal studies, safety evaluations and clinical trials. Oberg et al. also notes that the validity of different animal models can only be determined by evaluation of antiviral activity in patients. The teaching of Oberg et al. is also exemplified by Yarchoan et al.[4] Yarchoan et al. teaches that *in vitro* antiviral activity does not correlate with in vivo antiviral activity. Ergo, it is clear that *in vitro* data does not necessarily correlate with *in vivo* data and/or clinical observation. Furthermore, it is also well known in the art that the inhibitory activity of an antiviral agent against a particular virus cannot be equated with its inhibitory effect against another virus.[5]

More specifically, the development of HCV antiviral drugs has been limited by the absence of a stable cell-based system to support HCV replication and the paucity of effective animal models, as noted by Dev et al.[6] Dev et al. also summarizes the challenges that faces the development of an effective HCV antiviral drug, which includes: i) high genetic diversity and geographic distribution of HCV genotypes, antiviral agents must be effective against different genotypes; ii) the high rate of mutational change with in the HCV genome, which underscores the importance of drug resistance; and the lack of reliable, reproducible and efficient HCV cell culture systems and small animal models.

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[3] Oberg et al. Screening for new agents. Eur. J. Clin. Microbiol. Infect Dis., July 1990, Vol. 9, No. 7, p. 466-471.
[4] Yarchoan et al. Correlations between the in vitro and in vivo activity of anti-HIV agents: implications for future drug development. J. Enzyme Inhibition. 1992, Vol. 6, pp. 99-111.
[5] Wiltink et al. Antiviral drugs. Pharmaceutisch Weekblad Scientific edition. 1991, Vol. 13, No. 2, pp. 58-69.

Thus, in view of the challenges present in the art pertaining to the development of HCV antiviral pharmaceuticals and the limited teaching that is provided in the specification; the claims are rejected under 35 U.S.C. 112, first paragraph. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F. 2d 1557, 1562, 27 USPQ 2d 1510, 1513 (Fed. Cir. 1993).

Response to Applicant's Remarks

5. In response to the rejection set forth in the previous office action, Applicant submits:

a) Example 8 of the specification, and as explained in the attached Declaration of John S. Bomalaski et al. under 37 C.F.R. 1.132, arginine deiminase covalently bound to polyethylene glycol inhibits the replication of Hepatitis C virus (HCV) in vitro through a mechanism that does not involve or require the killing of hepatocellular carcinoma (HCC) cells.

The above submission has been considered, however, it is not found persuasive. The Office has reviewed Example 8 disclosed in the specification. This working

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[6] Dev et al. Antiviral Therapy: Future Treatment of Hepatitis C: What's around the Corner. Infect. Med. 2001, Vol. 21, No. 1: p. 28-36.

embodiment fails to demonstrate that the mechanism in which arginine deiminase covalently bound to polyethylene glycol (ADI-PEG) inhibits HCV replication does not involve or require the killing of hepatocellular carcinoma (HCC) cells. The working example clearly set forth that ADI-PEG kills HCC cells and inhibits HCV replication. Specifically, the working example notes that .335 IU/ml of ADI-PEG kills 50% of HCC cells.

In all, Applicant has not provided any convincing evidence demonstrating that the inhibition of HCV can be accomplished in the absence of HCC cells. In the instant, neither the specification nor the art teach the inhibition of HCV replication in the absence of HCC cells. The specification and the art only note the inhibition of HCV replication in the presence of HCC cells.

b) in view of the results obtained from clinical trials conducted on behalf of Phoenix Pharmacologics, Applicant, summarized on page 4 of Bomalaski's declaration, the specification enables methods for inhibiting the replication of various genotypes using ADI-PEG.

Applicant's submission has been considered, however, it is not found persuasive. The enablement requirement requires the specification to be enabling at the time the claimed invention is filed. In the instant, at the time the claimed invention is filed, the specification teaches that the claimed method is effective in inhibiting the replication of HCV 1b. The specification notes that the claimed method **failed** to inhibit the replication of HCV 2c. Thus, the specification is only enabling for a method of inhibiting the replication of HCV 1b, but not all other HCV genotypes, such as, 1a, 2a-c, 3a-b, 4, 5a

and 6. Furthermore, the evidence submitted in the Bomalaski's declaration clearly demonstrates that the claimed invention is not effective against the HCV genotypes 2, 2a/2c; 4, 1a and 1.

Conclusion

6. No claims are allowed.

7. As previously communicated to Applicant, the following is allowable: a method of inhibiting Hepatitis C viral (HCV) infection in an individual comprising administering an effective amount of a composition comprising an arginine deiminase bonded to polyethylene glycol to the individual to inhibit HCV replication the individual, wherein the individual is infected with HCV genotype 1b and 2a/2c, and diagnosed with hepatocellular carcinoma or have cells that do not express arigininosuccinate synthase (ASS) and are auxotrophic for arginine.

8. All claims are drawn to the same invention claimed prior to the filing of a Request for Continued Examination, RCE, and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

9. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Emily Le whose telephone number is (571) 272 0903. The examiner can normally be reached on Monday - Friday, 8 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (571) 272-0902. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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